PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 031392PC/KF	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. **PCT**/AU2004/001800	International filing date *(day/month/year)* 21 December 2004	Priority date *(day/month/year)* 23 December 2003

International Patent Classification (IPC) or national classification and IPC

Int. Cl.

C07H 5/10 (2006.01) ***A61P 7/00*** (2006.01) ***A61P 43/00*** (2006.01)

(continued in Supplemental Box)

Applicant

PROGEN INDUSTRIES LIMITED et al

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 7 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. [X] *(sent to the applicant and to the International Bureau)* a total of **5** sheets, as follows:
      - [ ] sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      - [X] sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.

   b. [ ] *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or table related thereto, in electronic form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).
4. This report contains indications relating to the following items:

[X]	Box No. I	Basis of the report
[ ]	Box No. II	Priority
[X]	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
[ ]	Box No. IV	Lack of unity of invention
[X]	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
[ ]	Box No. VI	Certain documents cited
[ ]	Box No. VII	Certain defects in the international application
[ ]	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
6 June 2005	24 March 2006
Name and mailing address of the IPEA/AU AUSTRALIAN PATENT OFFICE PO BOX 200, WODEN ACT 2606, AUSTRALIA E-mail address: pct@ipaustralia.gov.au Facsimile No. (02) 6285 3929	Authorized Officer **O.L. CHAI** Telephone No. (02) 6283

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/AU2004/001800

Box No. I Basis of the report

1. With regard to the **language,** this report is based on:

[X] The international application in the language in which it was filed

[ ] A translation of the international application into , which is the language of a translation furnished for the purposes of:

[ ] international search (under Rules 12.3(a) and 23.1 (b))

[ ] publication of the international application (under Rule 12.4(a))

[ ] international preliminary examination (Rules 55.2(a) and/or 55.3(a))

2. With regard to the **elements** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

[ ] the international application as originally filed/furnished

[X] the description:

pages **1-2, 5-50** as originally filed/furnished
pages* **3, 4** received by this Authority on **17 February 2006** with the letter of **17 February 2006**
pages* received by this Authority on with the letter of

[X] the claims:

pages as originally filed/furnished
pages* as amended (together with any statement) under Article 19
pages* **51-53** received by this Authority on **17 February 2006** with the letter of **17 February 2006**
pages* received by this Authority on with the letter of

[ ] the drawings:

pages as originally filed/furnished
pages* received by this Authority on with the letter of
pages* received by this Authority on with the letter of

[ ] a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing.

3. [ ] The amendments have resulted in the cancellation of:

[ ] the description, pages
[ ] the claims, Nos.
[ ] the drawings, sheets/figs
[ ] the sequence listing *(specify)*:
[ ] any table(s) related to the sequence listing *(specify)*:

4. [X] This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

[ ] the description, pages
[X] the claims, Nos. 7-8
[ ] the drawings, sheets/figs
[ ] the sequence listing *(specify)*:
[ ] any table(s) related to the sequence listing *(specify)*:

* *If item 4 applies, some or all of those sheets may be marked "superseded."*

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application

☒ claims Nos: **1, 3 (in part)**

because:

☐ the said international application, or the said claims Nos.
relate to the following subject matter which does not require an international preliminary examination *(specify)*:

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos.
are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos.
are so inadequately supported by the description that no meaningful opinion could be formed *(specify)*

☒ no international search report has been established for said claim Nos. **1, 3 (in part)**

☐ A meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

- ☐ Furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Preliminary Examining Authority in a form and manner acceptable to it.
- ☐ Furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Preliminary Examining Authority in a form and manner acceptable to it.
- ☐ Pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rules 13*ter*.1(a) or (b) and 13*ter*.2.

☐ A meaningful opinion could not be formed without the tables related to the sequence listings; the applicant did not, within the prescribed time limit, furnish such tables in electronic form complying with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions, and such tables were not available to the International Preliminary Examining Authority in a form and manner acceptable to it

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in electronic form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See Supplemental Box for further details.

Box No. V **Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Claims	**1-6, 9-16**	**YES**
	Claims		**NO**
Inventive step (IS)	Claims	**1-6, 9-16**	**YES**
	Claims		**NO**
Industrial applicability (IA)	Claims	**1-6, 9-16**	**YES**
	Claims		**NO**

2. Citations and explanations (Rule 70.7)

The following documents identified in the International Search Report have been considered for the purposes of this opinion:

D1 WO 1985/000973
D2 US 4459293
D3 WO 2003/038054
D4 Derwent Abstract Accession No 2000-100762/09
D5 Derwent Abstract Accession No 2001-337999/36
D6 Derwent Abstract Accession No 2000-116716/10
D7 WO 1993/024506
D8 WO 1997/018222
D9 Derwent Abstract Accession No 96-116981/12
D10 US 5700918
D11 Chemical Abstracts AN 140:314439
D12 Chemical Abstracts AN 141:54554
D13 Chemical Abstracts AN 138:82903
D14 Chemical Abstracts AN 133:267051
D15 Chemical Abstracts AN 131:322848
D16 Chemical Abstracts AN 129:107414

D11 and D12 are published after the priority date of the application. These documents may become relevant if the priority date of the application is found to be invalid at a later date.

Novelty (N) & Inventive Step (IS)

D1 discloses substituted phenyl-1-thio(poly-O-sulfo)-α(or β)-D-glucopyranosides, cation salts thereof and their use as modulators of the complement system involved with inflammation, coagulation, fibrinolysis, antibody-antigen reactions and other metabolic processes.

D2 discloses bis-[β-D-glucopyranosyl-1-thio (or sulfinyl or sulconyl)-arylene sulfate derivatives, the cation salts thereof, useful as modulators of the complement system involved with inflammation, coagulation, fibrinolysis, antibody-antigen reactions and other metabolic processes.

D4 discloses sulfated galactose compounds (I) and their pharmaceutical preparation.

(continued in Supplemental Box)

Supplemental Box

In case **the space in any of the preceding boxes is not sufficient.**

Continuation of: International Patent Classification (IPC)

Int. Cl.

A61K 31/70 (2006.01)	***A61P 7/02*** (2006.01)	***C07H 11/04*** (2006.01)
A61K 31/7012 (2006.01)	***A61P 29/00*** (2006.01)	***C07H 13/12*** (2006.01)
A61K 31/7016 (2006.01)	***A61P 31/00*** (2006.01)	***C07H 15/04*** (2006.01)
A61K 31/7028 (2006.01)	***A61P 35/00*** (2006.01)	***C07H 15/18*** (2006.01)

Action Date: 24 March 2006

Supplemental Box

In case **the space in any of the preceding boxes is not sufficient.**

Continuation of: item 4 of Box No. I

The subject matter of claims 7-8 goes beyond the disclosure in the international application as filed. Substituting one or more sulfate groups of the compounds of claim 1 with an alternative charged group would introduce new matter into the application. The report is established as if such amendment had not been made.

Supplemental Box

In case **the space in any of the preceding boxes is not sufficient.**

Continuation of: Box V

D5 discloses glucopyranose derivatives of formula (1) useful in the prevention and/or treatment of HIV infections, asthma, atopic dermatitis, and allergic and inflammatory disorders.

D6 discloses glucopyranose derivatives of formulae (I) useful in the treatment of HIV.

D7 discloses glucopyranose or galactopyranosy derivatives of formula I or II (gluand their use in modulating cell mediated immune responses eg for treating psoriasis, asthma, inducing tolerance to antigens.

D8 discloses glucopyranose or galactopyranosy derivatives of formulae I and II with immunosuppressive and tolerogenic activity for modulating cell mediated immune responses especially inflammation eg for treating psoriasis, asthma, dermatitis.

D9 discloses mono- or di- saccharide derivatives with galato or gluco stereochemistry.

D13 discloses a galactopyranosyl derivative as a pharmaceutical.

D14 discloses a galactopyranosyl derivative with anti-HIV activity.

D15 discloses a galactopyranosyl derivative with anti-inflammatory activity.

D16 discloses a galactopyranosyl derivative with anti-inflammatory activity.

The proviso in claim 1 excludes the stereochemistry of I to be a gluco or galacto, therefore D1, D2, D4-D9 and D13-D16 no longer anticipate the claims.

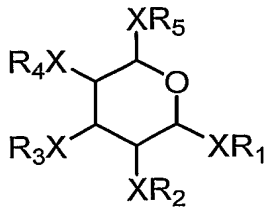
D10 discloses a moranoline derivative of formula (I) used for treating inflammation, immunopathy, viral infection and cancer. Claim 1 as amended is restricted to oxygen as the heteroatom in the ring of formula I. Therefore D10 no longer anticipates the claims.

D3 discloses compounds of Structures I–VI (see Figures 8-11) which no longer anticipate the amended claim 1.

In summary, none of D1-D10 and D13-D16 discloses all of the features of each of the independent claims. Therefore all of the claims are novel and meet the requirements of Article 33(2) PCT with regards to novelty. The subject matter of these claims is also considered not obvious and meets the requirements of Article 33(3) PCT with regards to inventive step.

Industrial Applicability (IA)

The invention defined in the claims is considered to meet the requirements of Industrial Applicability under Article 33(4) of the PCT because it can be made by, or used in, industry.



I

wherein:

each X is independently CH_2, C(O), N, O, S, S(O), $S(O)_2$, or is a bond; and

each of R_1 to R_5 is independently a bond or is selected from the group consisting of:

hydrogen;

halogen;

azide;

an R group defined as C1 to C8 alkyl or alkenyl, aryl or heteroaryl optionally further substituted by:

an alkoxy, aryl, heteroaryl or aryloxy;

-COOH, $-S(O)_2OH$;

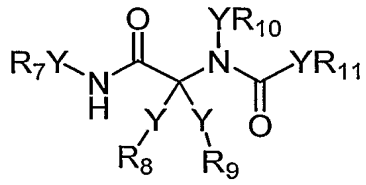
$-S(O)_2OH$, -S(O)OH, -S(O)R, $S(O)_2R$, $-S(O)_2NH_2$, $-S(O)_2OR$, -S(O)OR;

-C(O)R;

a heterocylic group further substituted by:

an alkyl, aryl, $-CH_2NHC(O)R$, $-CH_2N(C(O)R)_2$, or $-CH_2OR$;

a substructure of the following formula:



II

wherein at least one, but not more than two of R_7 to R_{11} is independently a structure according to formula **I**;

wherein:

each Y is independently a bond, H, R or -C(O)R as defined above; and

up to but no more than one of each of R_7 to R_{11} is independently a structure according to formula **II**, or each of R_7 to R_{11} is independently absent; or

and each R_1 to R_5 may be connected to a different R_1 to R_5 to form a fused bicyclic structure;

with the provisos that;

when R_1 is $-CH_3$, $-S(O)_2OH$ or -H at least one of R_2 to R_5 is not -H or $-S(O)_2OH$;

when a substructure of type **II** is not present and none of R_1-R_5 form an anhydro bridge, no more than two of R_1-R_5 are $-S(O)_2OH$ and the stereochemistry of **I** is not gluco or galacto.

According to a second embodiment of the invention, there is provided a pharmaceutical or veterinary composition for the prevention or treatment in a mammalian subject of a disorder resulting from angiogenesis, metastasis, inflammation, coagulation, thrombosis, and/or microbial infection, which composition comprises at least one compound according to the first embodiment together with a pharmaceutically or veterinarially acceptable carrier or diluent for said at least one compound.

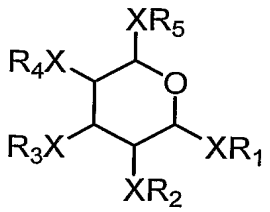
According to a third embodiment of the invention, there is provided the use of a compound according to the first embodiment in the manufacture of a medicament for the prevention or treatment in a mammalian subject of a disorder resulting from angiogenesis, metastasis, inflammation, coagulation, thrombosis, and/or microbial infection.

According to a fourth embodiment of the invention there is provided a method for the prevention or treatment in a mammalian subject of a disorder resulting from angiogenesis, metastasis, inflammation, coagulation, thrombosis, and/or microbial infection, which method comprises administering to the subject an effective amount of at least one compound according to the first embodiment, or a composition comprising said at least one compound.

In other embodiments of the invention, there are provided processes for synthesising the compounds according to the first embodiment as defined above.

CLAIMS

1. A compound of the formula



I

wherein:

each X is independently CH_2, C(O), N, O, S, S(O), $S(O)_2$, or is a bond; and

each of R_1 to R_5 is independently a bond or is selected from the group consisting of:

hydrogen;

halogen;

azide;

an R group defined as C1 to C8 alkyl or alkenyl, aryl or heteroaryl optionally further substituted by:

an alkoxy, aryl, heteroaryl or aryloxy;

-COOH, $-S(O)_2OH$;

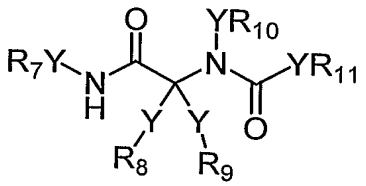
$-S(O)_2OH$, -S(O)OH, -S(O)R, $S(O)_2R$, $-S(O)_2NH_2$, $-S(O)_2OR$, -S(O)OR;

-C(O)R;

a heterocylic group further substituted by:

an alkyl, aryl, $-CH_2NHC(O)R$, $-CH_2N(C(O)R)_2$, or $-CH_2OR$;

a substructure of the following formula:



II

wherein at least one, but not more than two of R_7 to R_{11} is independently a structure according to formula **I**;

wherein:

each Y is independently a bond, H, R or -C(O)R as defined above; and

up to but no more than one of each of R_7 to R_{11} is independently a structure according to formula **II**, or each of R_7 to R_{11} is independently absent; or

each R_1 to R_5 is connected to a different R_1 to R_5 to form a fused bicyclic structure;

with the provisos that:

when R_1 is $-CH_3$, $-S(O)_2OH$ or -H at least one of R_2 to R_5 is not -H or $-S(O)_2OH$; and

when a substructure of type **II** is not present and none of R_1-R_5 form an anhydro bridge, no more than two of R_1-R_5 are $-S(O)_2OH$ and the stereochemistry of **I** is not gluco or galacto.

2. A compound according to claim 1, wherein said compound is PG2024, PG2037, PG2173, PG2198, as hereinbefore described.

3. A compound according to claim 1, wherein said compound is any one of the compounds of Tables 1-4 of the description.

4. A pharmaceutical or veterinary composition for the prevention or treatment in a mammalian subject of a disorder resulting from angiogenesis, metastasis, inflammation, coagulation, thrombosis, and/or microbial infection, which composition comprises at least one compound according to claim 1 together with a pharmaceutically or veterinarially acceptable carrier or diluent for said at least one compound.

5. The composition according to claim 4 which further includes a pharmaceutically or veterinarially acceptable excipient, buffer, stabiliser, isotonicising agent, preservative or antioxidant.

6. The composition according to claim 4, wherein said compound is present therein as an ester, a free acid or base, a hydrate, or a prodrug.

7. The composition according to claim 4, wherein one or more sulfate groups of said compound has been substituted for an alternate charged group.

8. The composition according to claim 7, wherein said alternate charged group is a phosphate, carboxylate or tetrazolyl anion.

9. Use of a compound according to claim 1 in the manufacture of a medicament for the prevention or treatment in a mammalian subject of a disorder resulting from angiogenesis, metastasis, inflammation, coagulation, thrombosis, and/or microbial infection.

10. The use according to claim 9, wherein said mammalian subject is a human subject.

11. A method for the prevention or treatment in a mammalian subject of a disorder resulting from angiogenesis, metastasis, inflammation, coagulation, thrombosis, and/or microbial infection, which method comprises administering to the subject an effective amount

of at least one compound according to claim 1, or a composition comprising said at least one compound.

12. The method according to claim 11 wherein said mammalian subject is a human subject.

13. The method according to claim 11, wherein said disorder resulting from angiogenesis is a proliferative retinopathy or angiogenesis resulting from the growth of a solid tumour.

14. The method according to claim 11, wherein said disorder resulting from inflammation is rheumatoid arthritis, multiple sclerosis, inflammatory bowel disease, allograft rejection or chronic asthma.

15. The method according to claim 11, wherein said disorder resulting from coagulation and/or thrombosis is deep venous thrombosis, pulmonary embolism, thrombotic stroke, peripheral arterial thrombosis, unstable angina or myocardial infarction.

16. The method according to claim 11, wherein said disorder resulting from viral infection is Herpes Simplex.